EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UCB PHARMA S.A. and CELLTECH R&D LIMITED,	)	
Plaintiffs,	)	
v.	)	C.A. No. 20-650 (CFC)
NEKTAR THERAPEUTICS,	)	
Defendant.	)	

PLAINTIFFS' INITIAL INVALIDITY CONTENTIONS

Pursuant to Paragraph 3 of the Court's Scheduling Order (D.I. 18), Plaintiffs UCB Pharma S.A. and Celltech R&D Limited (collectively, "UCB" or "Plaintiffs") hereby disclose their Initial Invalidity Contentions. UCB contends that each claim of U.S. Patent Nos. 7,767,784 (the "'784 patent"), 8,193,306 (the "'306 patent"), 8,461,295 (the "'295 patent"), and 8,809,489 (the "'489 patent") (collectively, the "Nektar Patents") is invalid under at least one or more of 35 U.S.C. §§ 101, 102, 103, 112, other equitable defenses, and/or the judicially-created doctrine of obviousness-type double patenting.

UCB reserves the right to supplement, amend, revise, correct, clarify, or otherwise modify these Initial Invalidity Contentions pursuant to the Federal Rules of Civil Procedure, the Court's Local Rules, or any other order or schedule entered by the Court. UCB further reserves the right to supplement, amend, revise, correct, clarify, or otherwise modify these Initial Invalidity Contentions based on further investigation or analysis, discovery of new prior art, or reevaluation of known prior art, or to the extent UCB becomes aware of any contentions by Nektar Therapeutics ("Nektar" or "Defendant") regarding secondary considerations of nonobviousness. UCB also provides these contentions without waiving any claim of privilege or work-product immunity.

I. GENERAL STATEMENTS

UCB's Initial Invalidity Contentions are based on UCB's knowledge, understanding, and belief as to the facts and information available as of the date of these Initial Invalidity Contentions. UCB has not yet fully completed its investigation, collection of information, discovery, or analysis relating to this action and additional discovery may require UCB to supplement or modify these contentions. As a non-limiting example, Nektar has not yet produced information about its manufacturing processes before the filing date of the Nektar Patents. For this and other reasons, including those set forth below, UCB reserves the right to further supplement or alter the positions taken and information disclosed in these Initial Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. UCB further reserves the right to introduce and use such supplemental materials at trial.

UCB provides the information below in a good faith effort to comply with the Local Rules and the Court's Scheduling Order. UCB reserves the right to amend, modify, and/or supplement these Initial Invalidity Contentions. Further, UCB reserves the right to prove the invalidity of the Nektar Patents' claims on bases other than those required to be disclosed in these Initial Invalidity Contentions.

A. Claim Construction

The Court has not yet construed any claims of the Nektar Patents. UCB reserves the right to identify other prior art or to supplement these Initial Invalidity Contentions because UCB's positions on invalidity of certain claims may depend on how the Court construes those claims. These Initial Invalidity Contentions are based, at least in part, on UCB's present understanding of the Nektar Patents' claims.

UCB takes no position on any matter of claim construction in these Initial Invalidity Contentions. UCB expressly reserves the right to propose any claim construction it considers appropriate and/or to contest any claim construction it considers inappropriate.

Similarly, nothing stated herein shall be treated as an admission or suggestion that UCB agrees with Nektar regarding either the scope of any Nektar Patent claim or the claim constructions advanced directly or implicitly by Nektar.

UCB anticipates that the Court's construction of claim terms may affect the scope of the Nektar Patents. Therefore, UCB reserves the right to supplement and/or modify these Initial Invalidity Contentions based upon any future claim construction ruling.

B. Ongoing Discovery and Disclosures

Discovery in this case is in its early stages and UCB's investigation, including its search for prior art, is ongoing. UCB therefore reserves the right to further supplement or alter the positions taken and information disclosed in these Initial Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. UCB hereby incorporates by reference the testimony of any fact witnesses that are deposed, that provide declarations, or that otherwise testify in this action. UCB also hereby incorporates by reference the forthcoming reports and testimony of its expert witnesses regarding invalidity of the patents.

UCB bases these Initial Invalidity Contentions on its current knowledge and understanding of the Nektar Patents' claims, the prior art, and other facts and information available as of the date of these contentions. UCB has not yet completed its investigation, collection of information, discovery, or analysis relating to this action, and additional discovery may require UCB to supplement or modify these contentions. For example, UCB has not yet deposed the named inventors of the Nektar Patents and/or other persons having potentially relevant information, but

will engage in this and other such discovery consistent with this Court's Orders. UCB therefore reserves the right to further supplement or alter the positions taken and information disclosed in these Initial Invalidity Contentions including, without limitation, the prior art and grounds of invalidity set forth herein, to take into account information or defenses that may come to light as a result of these continuing efforts. UCB further reserves the right to introduce and use such supplemental materials at trial.

Further, UCB intends to take discovery on public use and/or the on-sale bar under 35 U.S.C. § 102(b), additional prior art under 35 U.S.C. §§ 102 and 103, improper inventorship, applicant's failure to comply with 35 U.S.C. §§ 101 and 112, and/or the judicially-created doctrine of obviousness-type double patenting. UCB therefore reserves all rights to further supplement or amend these Initial Invalidity Contentions if further information becomes available.

C. Prior Art Identification and Citation

UCB identifies herein each item of prior art known at this time that it asserts invalidates, alone or in combination, each of the claims, under at least 35 U.S.C. §§ 102 and 103 from the perspective of a person having ordinary skill in the art ("POSA"). UCB also identified herein currently identified grounds of invalidity under 35 U.S.C. § 112 that it asserts invalidates the claims, as well as the judicially-created doctrine of obviousness-type double patenting. These Initial Invalidity Contentions, including the claim charts attached as Exhibits A-D, identify, on a claim-by-claim basis, where each limitation of each claim is found in the prior art. UCB identifies portions of prior art references that disclose the elements of the Nektar Patents' claims. To focus the issues, UCB identifies only limited portions of the cited references. That is, while UCB has identified at least one citation per element for each claim, UCB has not necessarily identified every disclosure in each cited reference of the same element. It should, however, be recognized that a skilled artisan would read a prior art reference as a whole and in the context of other publications,

literature, and general knowledge in the field. To understand and interpret any specific statement or disclosure in a prior art reference, a POSA would rely upon other information including other publications and general scientific or engineering knowledge. UCB therefore reserves the right to rely upon other portions of the prior art references not specifically cited herein, as well as on other publications and expert testimony to provide context and to aid understanding and interpretation of the identified portions. The absence of a particular reference in any of the claim charts for a particular feature is not a waiver or admission by UCB. UCB reserves the right to rely on any combination of the references listed and cited herein, even if not explicitly set forth below. UCB also reserves the right to rely upon other prior art references, other publications, and the testimony of experts to establish that the alleged inventions would have been obvious to a POSA, including by modifying or combining certain cited references.

D. Reservation of Rights

UCB reserves all rights to further supplement or modify these Initial Invalidity Contentions, including the prior art disclosed and stated grounds of invalidity, pursuant to the Court's Default Standard for Discovery and the Scheduling Order in this matter. In addition, UCB reserves the right to prove the invalidity of the Nektar Patents' claims on bases other than those required to be disclosed in these Initial Invalidity Contentions.

II. LEGAL STANDARDS

A. Invalidity Under § 102

One basis for establishing invalidity is anticipation by the prior art. The general test for anticipation requires that each and every limitation recited in a claim must be found in one item of prior art, either expressly or inherently, and arranged in the item of prior art in the same way as it is claimed, so that the disclosure effectively puts the public in possession of the invention. *Silicon Graphics, Inc. v. ATI Techs., Inc.*, 607 F.3d 784, 796-97 (Fed. Cir. 2010); *Impax Labs.,*

Inc. v. Aventis Pharms. Inc., 468 F.3d 1366, 1381 (Fed. Cir. 2006). A reference will be considered anticipatory if "it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995).

The law of anticipation does not require that a prior art reference explicitly disclose information that is inevitably present based on the express disclosure of the reference. Thus, "[a]n anticipatory reference . . . need not duplicate word for word what is in the claims. Anticipation can occur when a claimed invention is 'inherent' or otherwise implicit in the relevant reference." *Std. Havens Prods., Inc. v. Gencor Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991). While *inherent* anticipation may not be established by "probabilities or possibilities," if the prior art's disclosure is sufficient to show that "the natural result flowing from the operation as taught would result in the performance of the questioned function," the prior art disclosure should be regarded as sufficient to anticipate. *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed Cir. 2010) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (internal quotations omitted)). In addition, "products of identical chemical composition cannot have mutually exclusive properties." *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990). A chemical composition and its properties are inseparable. *Id.* Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *Id.*

Inherent anticipation does not require that a POSA at the time would have recognized the inherent disclosure. *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367-68 (Fed. Cir. 2006). Thus, with respect to claims to chemical compositions, the discovery of inherent properties of prior compositions that were unknown or unrecognized prior to the alleged

invention does not impart patentable novelty on the chemical composition. *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("it is immaterial, on the issue of novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties").

Further, a party may rely on extrinsic evidence to show a feature not explicitly disclosed in a prior art reference is inherently disclosed in that reference. The Federal Circuit has explained:

> [r]ecourse to extrinsic evidence is proper to determine whether a feature, while not explicitly discussed, is necessarily present in a reference. The evidence must make clear that the missing feature is necessarily present, and that it would be so recognized by persons of skill in the relevant art.

Telemac Cellular Corp. v. Topp Telecom, Inc., 247 F.3d 1316, 1328 (Fed. Cir. 2001). As such, a party asserting inherent anticipation may reference extrinsic evidence beyond the disclosure of the inherently anticipating reference to establish that an inherent feature or property is necessarily present.

To show that product-by-process claims (i.e., product claims that specify process steps by which that product is made) are anticipated, it is not necessary to show that the recited steps are in the prior art reference; rather, to be anticipatory, the reference need only disclose the resulting product. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317-20 (Fed. Cir. 2006).

B. Invalidity Under § 103

Under 35 U.S.C. § 103(a), a patent claim is obvious, and therefore invalid, "if the differences between the subject matter . . . patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." A party challenging the

validity of a claim under Section 103 must "prove by clear and convincing evidence that the claimed invention would have been obvious in view of the prior art." *Kahn v. Gen. Motors Corp.,* 135 F.3d 1472, 1479-80 (Fed. Cir. 1998); *Sciele Pharma Inc. v. Lupin Ltd.,* 684 F.3d 1253 (Fed. Cir. 2012); *i4i Ltd. P'ship v. Microsoft Corp.,* 598 F.3d 831,848 (Fed. Cir. 2010), *aff'd* 131 S.Ct. 2238 (June 9, 2011).

The obviousness analysis includes an assessment of (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claimed subject matter, and (4) any objective evidence of nonobviousness, often referred to as "secondary considerations." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation,* 676 F.3d 1063, 1068-69 (Fed. Cir. 2012); *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 17-18 (1966). The secondary considerations relating to the obviousness inquiry include commercial success, long felt but unsolved need, failure of others, copying, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention and skepticism of skilled artisans before the invention. *Power Integrations, Inc. v. Fairchild Semiconductor Int'!, Inc.,* 711 F.3d 1348, 1368 (Fed. Cir. 2013).

In order to determine obviousness, a court may look to: 1) "interrelated teachings of multiple patents;" 2) "the effects of demands known to the design community or present in the marketplace;" and 3) "the background knowledge possessed by a person having ordinary skill in the art." The determination should be based upon "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Intern. Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1740-41 (2007). The obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim," a court can take

into account "inferences and creative steps that a person of skill in the art would employ." *Id.* at 1741. However, obviousness cannot be proven by demonstrating that each element in a patent was independently known in the prior art. It is important to identify a reason that would have prompted a person of skill in the art in the relevant field to combine the elements in the way the patent in suit does. *See id.* "Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." *In re Merck & Co., Inc.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986) (internal citations omitted) (affirming obviousness of claims reciting method of treating depression with known compound in view of its structural similarity with a known anti-depressant).

In deciding obviousness, neither the actual motivation nor the purported motivation of the patentee controls. Rather, the objective reach of the claim is what matters. If the claim extends to what is obvious, then it is invalid under Section 103. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742. Additionally, if a combination was obvious to a person of ordinary skill in the art, but not to the actual patentee, then the alleged invention is still obvious. *Id.* at 1742. Furthermore, a claim may be found obvious if a skilled artisan may be able to fit together the teachings of multiple patents like a puzzle. *Id.* at 1742. *See also Bayer Schering Pharma AG v. Barr Labs., Inc.,* 575 F.3d 1341 (Fed. Cir. 2009); *Leapfrog Enters., Inc. v. Fisher-Price, Inc.,* 485 F.3d 1157, 1161-62 (Fed. Cir. 2007).

C. Invalidity Under § 112

Section 112 requires that the patent enable the full scope of the claims. Enablement requires that "the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled

when, "at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). In analyzing undue experimentation, courts use the factors enumerated in *Wands*: (1) the quantity of experimentation necessary, (2) how routine any necessary experimentation is in the relevant field, (3) whether the patent discloses specific working examples of the claimed invention, (4) the amount of guidance presented in the patent, (5) the nature and predictability of the field, (6) the level of ordinary skill, and (7) the scope of the claimed invention. 858 F.2d at 737.

Under 35 U.S.C. § 112, patent claims also must "particularly point[ ] out and distinctly claim[ ] the subject matter" regarded as the invention. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 902 (2014) (quoting 35 U.S.C. ¶ 112 ¶ 2). A claim is invalid for indefiniteness if its language, when read in light of the specification and prosecution history "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Id.* at 901. The standard "mandates clarity, while recognizing that absolute precision is unattainable." *Id.* at 910. Thus, the indefiniteness analysis "must take into account the inherent limitations of language" while being "precise enough to afford clear notice of what is claimed, thereby 'appris[ing] the public of what is still open to them.'" *Id.* (quoting *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996)). General principles of claim construction apply to indefiniteness allegations. *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377-78 (Fed. Cir. 2015).

D. Invalidity For Double Patenting, Including Under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

Pursuant to 35 U.S.C. § 101, an inventor may obtain only "a patent" for an invention. *See In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997) (Section 101 "permits only one patent to

be obtained for a single invention"). Courts enforce this policy via the double patenting doctrine which "precludes one person from obtaining more than one valid patent for either (a) the 'same invention,' or (b) an 'obvious' modification of the same invention." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). "If an inventor could obtain several sequential patents on the same invention, he could retain for himself the exclusive right to exclude or control the public's right to use the patented invention far beyond the term awarded to him under the patent laws." *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014). Such sequential terms would be an "unjustified timewise extension." *Takeda Pharm. Co., Ltd. v. Doll*, 561 F.3d 1372, 1375 (Fed. Cir. 2009) (quoting *In re Van Ornum*, 686 F.2d 937, 934-35 (C.C.P.A 1982)). In *Gilead*, the Federal Circuit held that, when considering whether a patent term has received an unjustified extension, it is the "expiration dates that should control," and determined that a later-issued, but earlier expiring, patent may serve as a double-patenting reference to an earlier-issued patent. 753 F.3d at 1215. Patents with different expiration dates due to patent term adjustment under Section 154 may be invalid for double-patenting. *Magna Elecs., Inc. v. TRW Automotive Holdings Corp.*, 12-cv-654, 2015 WL 11430786, at *4-5 (W.D. Mich. Dec. 10, 2015); *see also AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1373 (Fed. Cir. 2014).

III. THE NEKTAR PATENTS

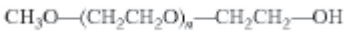
A. The '784 Patent

The '784 patent issued from U.S. Application No. 11/497,463, which was filed on July 31, 2006. It purportedly claims priority to U.S. Provisional Application No. 60/703,709, filed on July 29, 2005.

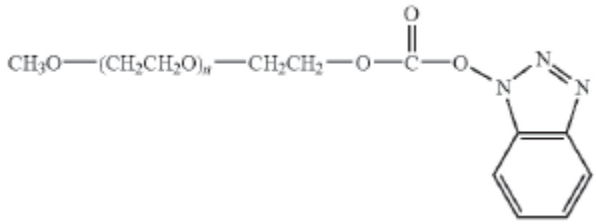
The '784 patent has a single claim, which is contended as invalid by UCB, reads:

1. A synthetic method comprising:

(a) combining a composition comprising an aprotic solvent and a hydroxy-terminated, water-soluble polymer having the following structure:



wherein (n) is an integer from 2 to about 4000, with a composition comprising di(1-benzotriazolyl)carbonate, wherein the composition comprising the di(1-benzotriazolyl)carbonate is added such that there is an excess of the di(1-benzotriazolyl)carbonate relative to the hydroxy-terminated, water-soluble polymer, to thereby result in a composition comprising an active carbonate ester of the water-soluble polymer having the following structure:



wherein (n) is an integer from 2 to about 4000, and unreacted di(1-benzotriazolyl)carbonate;

(b) adding a composition comprising a reactive molecule selected from the group consisting of water, hydrogen sulfide, and a lower alkyl monobasic amine to the composition comprising the active carbonate ester of a water-soluble polymer and unreacted di(1-benzotriazolyl)carbonate, wherein the composition comprising the reactive compound is added such that substantially all of the unreacted di(1-benzotriazolyl)carbonate is substantially consumed, wherein compositions resulting from step (a) are not isolated prior to conducting step (b).

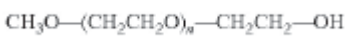
B. <u>The '306 Patent</u>

The '306 patent issued from U.S. Application No. 12/820,124, which was filed on June 21, 2010. It purportedly claims priority to U.S. Provisional Application No. 60/703,709, filed on July 29, 2005.

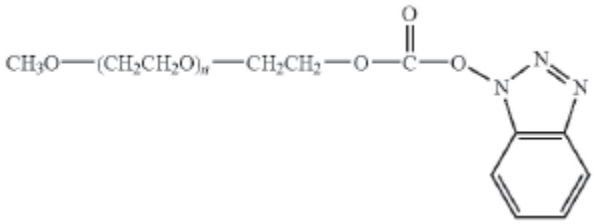
The '306 patent has four claims, of which claim 1 is the sole independent claim. Claims 1, 2, 4, which are contended as invalid by UCB, read:

1. A synthetic method comprising:

(a) combining a composition comprising an aprotic solvent and a hydroxy-terminated, water-soluble polymer having the following structure:



wherein (n) is an integer from 2 to about 4000, with a composition comprising di(1-benzotriazolyl)carbonate, wherein the composition comprising the di(1-benzotriazolyl)carbonate is added such that there is an excess of the di(1-benzotriazolyl)carbonate relative to the hydroxy-terminated, water-soluble polymer, to thereby result in a composition comprising an active carbonate ester of the water-soluble polymer having the following structure:



wherein (n) is an integer from 2 to about 4000, and unreacted di(1-benzotriazolyl)carbonate;

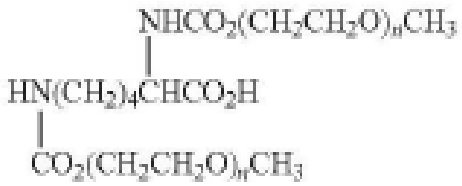
(b) adding a composition comprising a reactive molecule selected from the group consisting of water, hydrogen sulfate[1] and a lower alkyl monobasic amine to the composition comprising the active carbonate ester of a water-soluble polymer and unreacted di(1-benzotriazolyl)carbonate, wherein the composition comprising the reactive compound is added such that substantially all of the unreacted di(1-benzotriazolyl)carbonate is substantially consumed; and

(c) reacting the active carbonate ester of a water-soluble polymer lysine to form a polymeric lysine derivative.

2. The method as in claim 1, wherein the reactive molecule is selected from the group consisting of water, a lower alkyl monohydric alcohol, hydrogen sulfide, and a lower alkyl monobasic amine.

4. The method as in claim 1, wherein the polymeric lysine derivative has the following structure:

[1] Although element (b) of claim 1 uses the term "hydrogen sulfate," a Certificate of Correction for the '306 patent issued which corrected this term to "hydrogen sulfide."



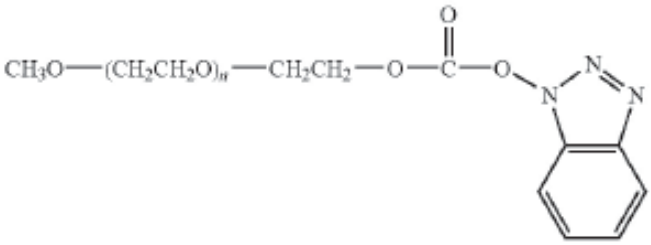
wherein each (n) is an integer from 2 to about 4000.

C. The ’295 Patent

The ’295 patent issued from U.S. Application No. 13/463,686, which was filed on May 3. 2012. It purportedly claims priority to U.S. Provisional Application No. 60/703,709, filed on July 29, 2005.

The ’295 patent has four claims of which claim 1 is the sole independent claim. Claims 1, 2, 4, which are contended as invalid by UCB, read:

> 1. The composition resulting from carrying out the synthetic method comprising:
>
> (a) combining a composition comprising an aprotic solvent and a hydroxy-terminated, water-soluble polymer having the following structure:
>
> 
>
> wherein (n) is an integer from 2 to about 4000, with a composition comprising di(1-benzotriazolyl)carbonate, wherein the composition comprising the di(1-benzotriazolyl)carbonate is added such that there is an excess of the di(1-benzotriazolyl)carbonate relative to the hydroxy-terminated, water-soluble polymer, to thereby result in a composition comprising an active carbonate ester of the water-soluble polymer having the following structure:



wherein (n) is an integer from 2 to about 4000, and unreacted di(1-benzotriazolyl)carbonate;

(b) adding a composition comprising a reactive molecule selected from the group consisting of water, hydrogen sulfide, and a lower alkyl monobasic amine to the composition comprising the active carbonate ester of a water-soluble polymer and unreacted di(1-benzotriazolyl)carbonate, wherein the composition comprising the reactive compound is added such that substantially all of the unreacted di(1-benzotriazolyl)carbonate is substantially consumed;

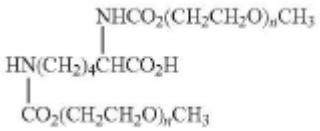
(c) reacting the active carbonate ester of a water-soluble polymer lysine to form a polymeric lysine derivative;

(d) reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent; and

(e) reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate.

2. The composition as in claim 2, wherein the reactive molecule is water.

4. The composition as in claim 1, wherein the polymeric lysine derivative has the following structure:



wherein each (n) is an integer from 2 to about 4000.

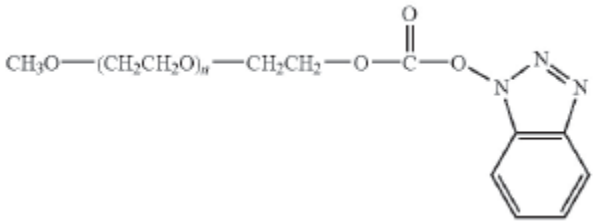
D. The '489 Patent

The '489 patent issued from U.S. Application No. 13/894,707, which was filed on May 15. 2013. It purportedly claims priority to U.S. Provisional Application No. 60/703,709, filed on July 29, 2005.

The '489 patent has four claims of which claim 1 is the sole independent claim. Claims 1, 2, 4, which are contended as invalid by UCB, read:

1. A synthetic method comprising:

(a) combining a composition comprising an aprotic solvent and mPEG (20,000 Da)-OH, with a composition comprising di(1-benzotriazolyl)carbonate, wherein the composition comprising the di(1-benzotriazolyl)carbonate is added such that there is an excess of the di(1-benzotriazolyl)carbonate relative to mPEG (20,000 Da)-OH, to thereby result in a composition comprising an active carbonate ester of the water-soluble polymer having the following structure:



and unreacted di(1-benzotriazolyl)carbonate;

(b) adding a composition comprising a reactive molecule selected from the group consisting of water, a lower alkyl monohydric alcohol, hydrogen sulfide and a lower alkyl monobasic amine to the composition comprising the active carbonate ester of a water-soluble polymer and unreacted di(1-benzotriazolyl)carbonate, wherein the composition comprising the reactive compound is added such that substantially all of the unreacted di(1-benzotriazolyl)carbonate is substantially consumed;

(c) reacting the active carbonate ester of a water-soluble polymer with lysine to form a polymeric lysine derivative;

(d) reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent; and

(e) reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate.

2. The method in claim 1, wherein the reactive molecule is water.

4. The method in claim 1, wherein the aprotic solvent is acetonitrile.

IV. PRIOR ART

UCB identifies the following prior art references in support of its invalidity contentions, which anticipate and/or render obvious, alone or in combination, the claims under 35 U.S.C. § 102

and/or 35 U.S.C. § 103. All references cited in this document are of the types known to be publicly available to and known and relied upon by a POSA.

UCB reserves the right to rely upon additional and/or different combinations of prior art than those presented here, using either the same of different prior art. UCB does not waive its right to assert an identified reference under another or an alternative basis of invalidity. UCB further reserves the right to supplement or amend its contentions as discovery is ongoing. UCB further reserves the right to rely on, and hereby incorporates by reference, prior art identified or discussed in the file histories of the patents-in-suit, any inter partes review or other Patent and Trademark Office proceeding, or any related patents or patent applications, including foreign prosecutions, and any prior art and/or arguments identified in related actions or proceedings, foreign or domestic.

The prior art disclosures identified in these contentions should be read as they would have been understood by a POSA with all of the background knowledge that such a person would have possessed by the applicable priority date of the Nektar Patents.[2] To the extent a reference is listed below but not set forth as, or in, a ground of invalidity, UCB reserves the right to rely on the listed prior art as forming the background knowledge of a POSA, and supporting that person's motivation to combine the prior art with a reasonable expectation of success. Further, to the extent a reference is cited below for one or several of its teachings, UCB reserves the right to rely on that reference for any other aspect of its teaching.

[2] For the purposes of these contentions, UCB assumes the priority date of the Nektar Patents is July 29, 2005. UCB, however, reserves the right to contest that date.

In addition to the below, UCB identifies the references cited on the face of the Nektar Patents, the admitted prior art references in the specifications and/or prosecution histories of the Nektar Patents, and the prosecution history of any related patents and/or applications.

Number/Citation	Country of Origin	Issue/ Publication Date
U.S. 5,932,462	United States	Aug. 3, 1999
U.S. 6,376,604	United States	Apr. 23, 2002
U.S. 6,624,246	United States	Sept. 23, 2003
U.S. 6,710,125	United States	Mar. 23, 2004
U.S. 7,101,932 (Published as US 2004/0157991)	United States	Published Aug. 12, 2004
WO1998/25971	United Kingdom	June 18, 1998
WO2001/94585	United Kingdom	Dec. 13, 2001
WO2004/047871	United States	June 10, 2004
Cooper & Williams, *Hydrolysis of Simple Aromatic Esters and Carbonates*, 27 J. Org. Chem. 3717 (1962)		1962
Shearwater Polymers, Functionalized Biocompatible Polymers for Research and Pharmaceuticals: Polyethylene Glycol and Derivatives (2000)		2000
Mitsuru Ueda, *et al.*, *1, 1'-[Carbonyldioxy]dibenzotriazole: A New, Reactive Condensing Agent for the Synthesis of Amides, Esters, and Dipeptides*, 11 Synthesis (Stuttgart) 908-909 (1983)		1983
GB 2 158 432 B	United Kingdom	Published Nov. 13, 1985
Merck Specification for Dichloromethane		
Merck Specification for Diethyl Ether		
Charles Beauchamp, *et al.*, *A New Procedure for the Synthesis of Polyethylene Glycol-Protein Adducts; Effects on Function, Receptor Recognition, and Clearance of Superoxide Dusmutase, Lactoferrin, and α_2-Macroglobulin*, 141 Analytical Biochemistry 25-33 (1983)		1983
Donald Elbert & Jeffrey Hubbell, *Self-assembly and steric stabilization at heterogenous, biological surfaces using adsorbing block copolymers*, 5(3) Chemistry & Biology 177-183 (1998)		1998
U.S. Publication No. 2005/0220753	United States	Oct. 6, 2005

Number/Citation	Country of Origin	Issue/ Publication Date
Talia Miron & Meir Wilchek, *A Simplified Method for the Preparation of Succinimidyl Carbonate Polyethylene Glycol for Coupling to Proteins*, 4 Bioconjugate Chem. 568-569 (1993)		1993
O. Schiavon, *et al.*, *PEG-Ara-C conjugates for controlled release*, 39 European J. of Med. Chem. 123-133 (2004)		Feb. 2004
Michelle Nijs, *et al.*, *Acylation of Amino Functions of Proteins with Monomethoxypoly (ethylene glycol)-N-Succinimide Carbonate*, 49 Applied Biochemistry and Biotechnology 75-91 (1994)		1994
U.S. Patent No. 6,515,100	United States	Feb. 4, 2003
Samuel Zalipsky, *Alkyl succinimidyl carbonates undergo Lossen rearrangement in basic buffers*, 34(1) Chem Commun. 69-70 (1998)		1998
U.S. 5,304,549	United States	Apr. 19, 1994
Rolf Paul & George Anderson, *N,N'-Carbonyldiimidazole in Peptide Synthesis. III. A Synthesis of Isoleucine-5 Angiotension II Amide-1*, 27 J. OF ORGANIC CHEMISTRY 2094-99 (June 1962)		1962
Luciana Sartore, *et al.*, *Enzyme Modification by MPEG with an Amino Acid or Peptide as Spacer Arms*, 27 APPL. BIOCHEM. BIOTECHNOL. 45-54 (1991)		1991

UCB also identifies Nektar's manufacturing processes, and any sales or offers of sales related to products produced by Nektar's manufacturing processes, as prior art to the Nektar Patents.

For the sake of example only, the following describes some of the teaching of these references:

A. U.S. 5,932,462

U.S. Patent No. 5,932,462 (the "'462 patent") was published August 3, 1999, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The ’462 patent describes multi-armed, monofunctional, and hydrolytically stable polymers, a specific example of which is a methoxy-PEG (“mPEG”) disubstituted lysine. ’462 patent at Abstract, 4:1-8. Purified mPEG disubstituted lysine may be produced in accordance with a two-step procedure (12:40-15:54), then activated with N-hydroxysuccinimide to product mPEG-disubstituted lysine activated as the succinimidyl ester. *Id.* at 12:40-15:54, 28:32-59. The activated, two-armed mPEG-disubstituted lysines of the invention may be used to modify enzymes. *Id.* at 30:65-31:3.

B. U.S. 6,376,604

U.S. Patent No. 6,376,604 (the “’604 patent”) was published April 23, 2002, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The ’604 patent describes a method for preparing a 1-benzotriazolylcarbonate ester of a water-soluble and non-peptidic polymer by reacting a terminal hydroxyl group of a water-soluble and non-peptidic polymer with di-BTC in the presence of an amine base and an organic solvent. ’604 patent at Abstract. The ’604 patent specifically describes combining a solution of $mPEG_{20,000}$ with di-BTC and an excess of di-BTC in the aprotic solvent acetonitrile. *Id.* at 7:47-62. It further describes the synthesis of PEG_2Acid via reaction of $mPEG_{20,000}BTC$ (“mPEG-BTC”) and lysine. *Id.* at 7:63-8:16.

C. U.S. 6,624,246

U.S. Patent No. 6,624,246 (the “’246 patent”) was published July 25, 2002, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The ’246 patent describes a method for preparing a 1-benzotriazolylcarbonate ester of a water-soluble and non-peptidic polymer by reacting a terminal hydroxyl group of a water-soluble

and non-peptidic polymer with di-BTC in the presence of an amine base and an organic solvent. '246 patent at Abstract. The '246 patent specifically describes combining a solution of $mPEG_{20,000}$ with di-BTC and an excess of di-BTC in the aprotic solvent acetonitrile. *Id.* at 7:63-8:11. It further describes the synthesis of PEG_2Acid via reaction of $mPEG_{20,000}BTC$ ("mPEG-BTC") and lysine. *Id.* at 8:12-32.

D. U.S. 6,710,125

U.S. Patent No. 6,710,125 (the "'125 patent") was published July 4, 2002, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The '125 patent describes a method for preparing a 1-benzotriazolylcarbonate ester of a water-soluble and non-peptidic polymer by reacting a terminal hydroxyl group of a water-soluble and non-peptidic polymer with di-BTC in the presence of an amine base and an organic solvent. '125 patent at Abstract. The '125 patent specifically describes combining a solution of $mPEG_{20,000}$ with di-BTC and an excess of di-BTC in the aprotic solvent acetonitrile. *Id.* at 7:63-8:11. It further describes the synthesis of PEG_2Acid via reaction of $mPEG_{20,000}BTC$ ("mPEG-BTC") and lysine. *Id.* at 8:12-31.

E. U.S. 7,101,932 and US 2004/0157991

U.S. 7,101,932 (the "'932 patent") was published as US 2004/0157991 on August 12, 2004, and this is prior art under at least § 102(a). The '932 patent itself issued on September 5, 2006 from an application filed on December 2, 2003 and is therefore prior art under § 102(e).

The '932 patent describes a method for preparing a 1-benzotriazolylcarbonate ester of a water-soluble and non-peptidic polymer by reacting a terminal hydroxyl group of a water-soluble and non-peptidic polymer with di-BTC in the presence of an amine base and an organic solvent. '932 patent at Abstract. The '932 patent specifically describes combining a solution of $mPEG_{20,000}$

with di-BTC and an excess of di-BTC in the aprotic solvent acetonitrile. *Id.* at 7:52-8:2. It further describes the synthesis of PEG_2Acid via reaction of $mPEG_{20,000}BTC$ ("mPEG-BTC") and lysine. *Id.* at 8:4-24.

F. WO 98/25971

WO 98/25971 ("WO '971") was published June 18, 1998, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

WO '971 describes monovalent antibody fragments which has one or more polymer molecules site-specifically attached through a Sulphur atom of a cysteine residue located outside of the variable region domain of the antibody. WO '971 at Abstract. Example 2 of WO '971 discloses "Fab'-PEG" conjugates formed by reacting an activated antibody fragment with a "40kDa PEG-maleimide derivative [with] a branched structure comprising two 20kDa PEG chains linked through a lysine derivative to a maleimide group." *Id.* at 20:18-34.

G. WO 01/94585

WO 01/94585 ("WO '585") was published December 13, 2001, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

WO '585 describes antibody molecules containing at least one complementarily determining region derived from a mouse monoclonal antibody having specificity for human tumor necrosis factor-α. WO '585 at Abstract. WO '585 discloses PEGylation of modified Fab fragments with a maleimide group covalently linked to a single thiol group in a modified hinge region and a lysine residue covalently linked to the maleimide group, wherein the total molecular weight of the effector molecule is approximately 40,000 Da. *Id.* at 9:28-10:3.

H. WO 04/047871

WO 04/047871 ("WO '871") was published December 13, 2001, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

WO '871 describes modified natriuretic compounds and conjugates thereof. WO '871 at Abstract. WO '871 specifically discloses dissolving monodispersed branched MPEG (1.21 mmol) in acetonitrile (20 mL) and disuccinimidyl carbonate (1.82 mmol). Triethylamine was added, and the reaction was stirred overnight, after which the reaction was evaporated to dryness and then dissolved in saturated $NaHCO_3$, washed ethyl acetate, dried $MgSO_4$, and evaporated to dryness. WO '871 at 51:4-15.

I. Cooper

Cooper & Williams, *Hydrolysis of Simple Aromatic Esters and Carbonates*, 27 J. Org. Chem. 3717 (1962) ("Cooper") was published October 1962, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Cooper describes hydrolysis of simple aromatic esters and carbonates. Cooper at 3717. Cooper discloses that diaryl carbonates hydrolyze quickly in a variety of aqueous environments, and significantly faster than their alkyl counterparts. *Id*. at 3718.

J. Shearwater Catalog

Shearwater Polymers, Functionalized Biocompatible Polymers for Research and Pharmaceuticals: Polyethylene Glycol and Derivatives (2000) ("Shearwater Catalog") was published in 2000, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The Shearwater Catalog describes polyethylene glycol and its derivatives, and lists them for sale. Shearwater Catalog at 1. The Shearwater Catalog discloses the hydrolysis half-lives of several PEG active esters at pH 8 and 25ºC, including mPEG-BTC. *Id.* at 45.

K. Ueda

Mitsuru Ueda, *et al.*, *1, 1'-[Carbonyldioxy]dibenzotriazole: A New, Reactive Condensing Agent for the Synthesis of Amides, Esters, and Dipeptides*, 11 Synthesis (Stuttgart) 908-909 (1983) ("Ueda") was published in 1983, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Ueda describes a reaction involving di-BTC followed by a work-up with water.

L. GB 2 158 432 B

GB 2 158 432 B was published in November 1985 as an application and in October 1987 as a patent, more than one year before the asserted priority dates of all of the Nektar Patents, and this is prior art under at least §§ 102(a) and 102(b).

GB 2 158 432 B describes a reaction involving di-BTC followed by a work-up with water. *Id.* at 10:10-24

M. Beauchamp

Charles Beauchamp, *et al.*, *A New Procedure for the Synthesis of Polyethylene Glycol-Protein Adducts; Effects on Function, Receptor Recognition, and Clearance of Superoxide Dusmutase, Lactoferrin, and α_2-Macroglobulin*, 141 Analytical Biochemistry 25-33 (1983) ("Beauchamp") was published in 1983, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Beauchamp discloses the preparation of active carbonate esters of PEG-5 or PEG-20 using PEG-5 or PEG-20 at a concentration of 5 mM and 1,1'-carbonyldiimidazole at a concentration of 500 mM in dioxane, i.e. an aprotic solvent. *Id.* at 27. 1,1'-carbonyldiimidazole

is listed as activated carbonate reagent in claim 1 of EP'350. It is used in a tenfold excess in comparison to PEG-5 or PEG-20. In the product mixture, not only the activated derivative of PEG-5 or PEG-20 will be obtained, but also unreacted amounts of 1,1'carbonyldiimidazole. After the reaction, the product mixture is "dialyzed against H_2O" (*id.* at 27) and afterwards lyophilized. The dialysis brings the sample into contact with water due to osmotic pressure, so that a consuming step occurs prior to recovering the desired active carbonate ester of PEG by lyophilization. Since dialysis is carried out extensively, a sufficient amount of water is added to the composition such that the unreacted carbonate reagent is consumed.

N. Elbert

Donald Elbert & Jeffrey Hubbell, *Self-assembly and steric stabilization at heterogenous, biological surfaces using adsorbing block copolymers*, 5(3) Chemistry & Biology 177-183 (1998) ("Elbert") was published in 1998, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Elbert describes a reaction generating the succinimidyl carbonate of PEG, via a reaction of "1 equivalent of dry PEG with 5 equivalents of disuccinimidyl carbonate." *Id.* at 181. The reaction was performed in "anhydrous DMF." *Id.*

O. Ji

U.S. Publication No. 2005/0220753 ("Ji') was published on October 6, 2005 and claims priority to an application filed on March 20, 2003, and so is prior art under at least § 102(e).

Ji describes a reaction of methoxypolyethylene glycol and N,N'-disuccinimidyl carbonate in acetonitrile. *Id.* at ¶ [0070]. The reference also discloses the use of dry pyridine in the reaction. *Id.*

P. Miron

Talia Miron & Meir Wilchek, *A Simplified Method for the Preparation of Succinimidyl Carbonate Polyethylene Glycol for Coupling to Proteins*, 4 Bioconjugate Chem. 568-569 (1993) ("Miron") was published in 1993, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Miron describes a reaction of N, N'-disuccinimidyl carbonate with methoxypolyethylene glycol. *Id.* at 568. Miron makes clear that steps are taken to keep the reaction anhydrous, including using dry solvent and dry storage of the final product. *Id.* at 568-569.

Q. Schiavon

O. Schiavon, *et al.*, *PEG-Ara-C conjugates for controlled release*, 39 European J. of Med. Chem. 123-133 (2004) ("Schiavon") was published in February 2004, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Schiavon describes the preparation of mPEG-(p-nitrophenyl carbonate). *Id.* at 129, 125. In that reaction, 0.2 mmol of monomethyl poly(ethylene glycol) was reacted with a three-fold excess of p-nitrophenyl chloroformate. *Id*. at 129. The reaction uses dehydrated solvents. *Id.*

R. Nijs

Michelle Nijs, *et al.*, *Acylation of Amino Functions of Proteins with Monomethoxypoly (ethylene glycol)-N-Succinimide Carbonate*, 49 Applied Biochemistry and Biotechnology 75-91 (1994) ("Nijs") was published in 1994, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Nijs describes a reaction between mPEG and excess N,N'-disuccinimidyl carbonate. *Id.* at 88. The reaction is performed under anhydrous conditions. *See id.*

S. U.S. 6,515,100

U.S. Patent No. 6,515,100 (the "'100 patent") issued on February 4, 2003, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The '100 patent discloses, *inter alia*, discloses preparation of PEG and related polymer derivatives, Abstract, and azeotropically distilling 1.25 g CH_3-O-PEG-O-$(CH_2)_n$-CO_2-PEG-OH 5400 with 100 ml acetonitrile, and adding 245 mg, *i.e.*, a molar excess, of disuccinimidyl carbonate. *Id.* at 16:59-64.

T. Zalipsky

Samuel Zalipsky, *Alkyl succinimidyl carbonates undergo Lossen rearrangement in basic buffers*, 34(1) Chem Commun. 69-70 (1998) ("Zalipsky") was published in 1998, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Zalipsky describes reactions of succinimidyl carbonate with polyethylene glycol. *Id.* at 69-70. Zalipsky further describes the hydrolysis succinimidyl carbonate and PEG-succinimidyl carbonate. *Id.*

U. U.S. 5,304,549

U.S. Patent No. 5,304,549 (the "'549 patent") was published July 25, 2002, more than one year before the alleged priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

The '549 patent describes a reaction of N-benzyloxycarbonyl-L-2-(tert-butyl)glycine (217 µM) and di(1-benzotriazolyl) carbonate (309 µM). *Id.* at 37:24-28. (S)-α-methylbenzylamine was then added to the reaction before the entire solution was washed with saturated sodium hydrogen carbonate and 1M hydrochloric acid. *Id.* at 37:28-35.

V. Paul

Rolf Paul & George Anderson, *N,N'-Carbonyldiimidazole in Peptide Synthesis. III. A Synthesis of Isoleucine-5 Angiotension II Amide-1*, 27 J. OF ORGANIC CHEMISTRY 2094-99 (June 1962) ("Paul") was published in 1962, more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Paul describes a reaction sequence comprising the steps of:

(a) reacting an excess of N,N'-carbonyl diimidazole with the carboxylic acid group of an amino acid to form an acylimidazole as activated intermediate;

(b) adding water as reactive molecule to destroy unreacted N,N'-carbonyl diimidazole, and

(c) adding an amine, *e.g.*, an amino acid with a protected carboxylic acid group, to form an amide bond with the acylimidazole.

Paul explicitly describes this strategy:

> If an amino- or carboxy-protected peptide or amino acid is hydrated with an undetermined amount of water it presents a problem in the use of N,N'-carbonyldiimidazole since an excess of the reagent gives ureas with the amine portion. We have solved this problem in several cases by treating the acid portion with an *excess of reagent*, cooling the solution of the acyl imidazole to -5°C, *adding a small amount of water to destroy the excess reagent* and then adding the amine.

*Id.*at 2096.

W. Sartore

Luciana Sartore, *et al.*, *Enzyme Modification by MPEG with an Amino Acid or Peptide as Spacer Arms*, 27 APPL. BIOCHEM. BIOTECHNOL. 45-54 (1991) ("Sartore") was published in 1991,

more than one year before the asserted priority dates of all of the Nektar Patents, and thus is prior art under at least §§ 102(a) and 102(b).

Sartore descries, *inter alia*, a reaction between mPEG-OH and excess 4-nitrophenyl chloroformate, an activating agent, in anhydrous methylene chloride. *Id.* at 47.

V. THE CLAIMS OF THE NEKTAR PATENTS ARE ANTICIPATED BY THE PRIOR ART

A. The '604 patent anticipates claims of the Nektar Patents

Claim 1 of the '784 patent, claims 1, 2, and 4 of the '306 patent, claims 1, 2, and 4 of the '489 patent, and claims 1, 2, and 4 of the '295 patent are invalid as anticipated under 35 U.S.C. § 102 by the '604 patent. With regards to limitation (b) of claim 1 of the '784 patent, '306 patent, '489 patent, and '295 patent as set forth in Exhibits A-D, the '604 patent discloses adding the solvents methylene chloride and ethyl ether to a composition of unreacted di-BTC and a 1-benzotriazolyl carbonate ester of m-PEG. '604 patent at Example 2. These solvents inherently contain water, as evidenced by their technical specifications; technical grade methylene chloride comprises water in an amount of ≤ 0.10%, and technical grade diethyl ether comprises water in an amount of ≤ 0.2%. *See* Merck Specification for Dichloromethane EMPLURA®, pg. 1; Merck Specification for Diethyl Ether EMPLURA®, pg. 1. Moreover, neither solvent is specified as being water-free in the '604 patent. The water contained in these solvents is thus the reactive molecule that is added to the composition to consume any unreacted di-BTC; therefore, the '604 patent inherently anticipates limitation (b) of the '784 patent. The remainder of the limitations of the Nektar Patents are disclosed by the '604 patent, as set forth in Exhibits A-D. Thus, the '604 patent anticipates claim 1 of the '784 patent, claims 1, 2, and 4 of the '306 patent, claims 1, 2, and 4 of the '489 patent, and claims 1, 2, and 4 of the '295 patent.

B. WO '971 anticipates claims of the '295 patent

The claims of the '295 patent are invalid as anticipated under 35 U.S.C. § 102 by WO '971.

(i) Claim 1

WO '971 discloses forming "Fab'-PEG" conjugates by reacting an antibody fragment with a "40kDa PEG-maleimide derivative [with] a branched structure comprising two 20kDa PEG chains linked through a lysine derivative to a maleimide group." *E.g.*, WO '971 at 20:18-34. These conjugates are products that could result from following the steps of claim 1; thus, WO '971 anticipates claim 1 of the '295 patent. *See SmithKline Beecham*, 439 F.3d at 1317-20.

(ii) Claims 2-4

Claim 2-4 require additional manufacturing steps – *e.g.*, that the "reactive molecule" in step (b) of claim 1 be water, that the reactive molecule be selected from hydroxyalkyl attached to a solid support, and that the polymeric lysine derivative have a certain structure – but those steps do not alter the final composition of the claims. Thus, WO '971 anticipates claim 2-4 of the '295 patent for the same reason it anticipates claim 1.

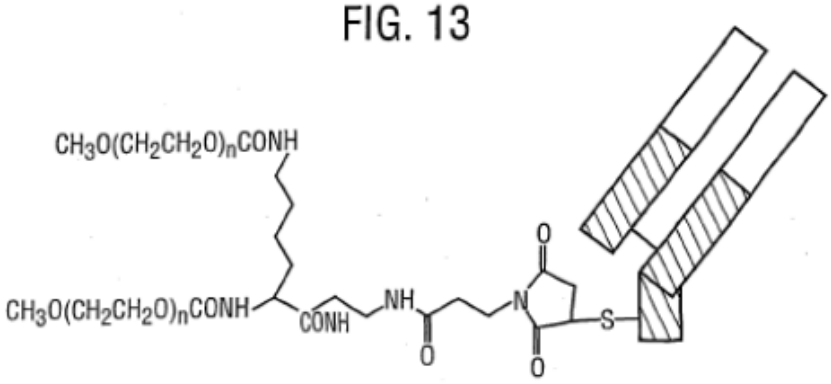
C. WO '585 anticipates the claims of the '295 patent

The claims of the '295 patent are invalid as anticipated under 35 U.S.C. § 102 by WO '585.

(i) Claim 1

WO '585 discloses PEGylated modified Fab fragments – i.e., PEG is covalently attached to the Fab fragments. WO '585 at 9:28-29. The preferred PEGylated modified Fab fragment of the invention is as follows:

FIG. 13



*Id.*at 9:30-31; Figure 13. As shown in this figure, the modified Fab fragment has a maleimide group covalently linked to a single thiol group in a modified hinge region and a lysine residue covalently linked to the maleimide group. *Id.* at 9:31-33. An mPEG polymer is attached to each of the amine groups on the lysine residue, each mPEG group having a molecular weight of approximately 20,000 Da, for a total molecular weight of approximately 40,000 Da. *Id*. at 9:33-10:3. This product is described as CDP870. *E.g.*, *id.* at 9:30-10:6. This structure above is a composition according to claim 1 of the '295 patent. Thus, WO '585 anticipates claim 1 of the '295 patent. *See SmithKline Beecham*, 439 F.3d at 1317-20.

(ii) Claims 2-4

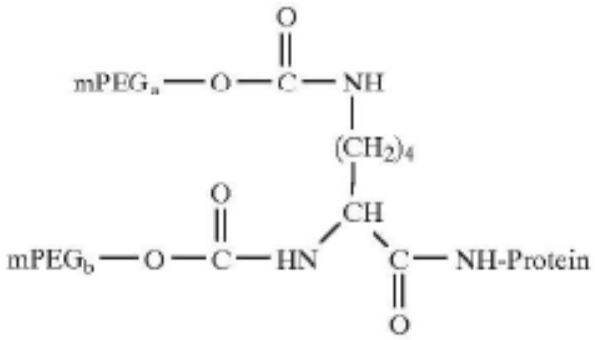
Claims 2-4 require additional manufacturing steps – *e.g.*, that the "reactive molecule" in step (b) of claim 1 be water, that the reactive molecule be selected from hydroxyalkyl attached to a solid support, and that the polymeric lysine derivative have a certain structure – but those steps still lead to a composition which is anticipated by WO '585. Thus, WO '585 anticipates claim 2-4 of the '295 patent for the same reason it anticipates claim 1.

D. The '462 patent anticipates the claims of the '295 patent

UCB contends that claims of the '295 patent are invalid as anticipated under 35 U.S.C. § 102 by the '462 patent.

(i) Claim 1

The '462 patent discloses multi-armed, monofunctional, and hydrolytically stable polymers, a specific example of which is a methoxy-PEG ("mPEG") disubstituted lysine. '462 patent at Abstract, 4:1-8. The '462 patent discloses a water-soluble polymer-active agent conjugate as follows:



Id. at 30:65-31:26. The mPEG-OH used to prepare the succinimidylcarbonate mPEG for disubstitution of lysine has a molecular weight of 20,000. *Id*. at 17:3-35. This structure above is a product that could result from the method of claim 1. Thus, the '462 patent anticipates claim 1 of the '295 patent. *See SmithKline Beecham*, 439 F.3d at 1317-20.

(ii) Claims 2-4

Claim 2-4 require additional manufacturing steps – *e.g.*, that the "reactive molecule" in step (b) of claim 1 be water, that the reactive molecule be selected from hydroxyalkyl attached to a solid support, and that the polymeric lysine derivative have a certain structure – but those steps do not alter the final composition of the claims. Thus, the '462 patent anticipates claim 2-4 of the '295 patent for the same reason it anticipates claim 1.

E. Claims of the Nektar Patents are invalid as anticipated due to sales and/or offers for sale made prior to July 29, 2005

Claim 1 of the '784 patent, claims 1, 2, and 4 of the '306 patent, claims 1, 2, and 4 of the '489 patent, and claims 1, 2, and 4 of the '295 patent are invalid due to sales of PEG made via the claimed processes prior to the Nektar patent's priority date. Those sales and/or offers for sale including, at least, the following:

Item Sold or Offered For Sale	Date of Sale or Offer For Sale	Entity That Made the Sale or Offer For Sale
PEG generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Celltech and/or UCB concerning, at least, the product Cimzia®	December 2000 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent

UCB also asserts that the following sales and/or offers for sale made by Nektar may constitute anticipatory sales and/or offers for sale as to claim 1 of the '784 patent, claims 1, 2, and 4 of the '306 patent, claims 1, 2, and 4 of the '489 patent, and claims 1, 2, and 4 of the '295 patent. Further information, which UCB will seek through discovery, is necessary due to non-public nature of such sales and/offers for sales, which include, at least:

Item Sold or Offered For Sale	Date of Sale or Offer For Sale	Entity That Made the Sale or Offer For Sale
PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Hoffmann-La Roche Ltd. concerning, at least, the product Pegasys®	On or around February 1997 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent
PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Amgen Inc. concerning, at least, the product Neulasta®	On or around July 1995 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent
PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Schering-Plough Corporation concerning, at least, the product Peg-Intron®	On or around February 2000 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent
PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Eyetech Pharmaceuticals, Inc. concerning, at least, the product Macugen®	On or around February 2002 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent

PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Sensus Drug Development Corporation concerning, at least, the product Somavert®	On or around January 2000 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent
PEG which may be generated, in part, via the processes claimed in the '784 and/or '306 patents, and sold and/or offered for sale to Bayer, Baxter, and/or Baxalta concerning, at least, its Factor VIII product	On or around December 2003 – July 2005	Nektar and/or Shearwater Corporation, and/or any related entity or agent, or entity or agent acting on behalf of Nektar, Shearwater Corporation, or any related entity or agent

If other sales and/or offers for sale become known to UCB during the discovery process, including those involving parties and/or products beyond those identified above, UCB reserves the right to assert that such sales and/or offers for sale are anticipatory.

VI. THE CLAIMS OF THE NEKTAR PATENTS ARE INVALID AS OBVIOUS

The claims of the Nektar Patents would have been obvious over the prior art. A POSA would have been motivated to combine the references identified above to arrive at the claimed subject matter and would have had a reasonable expectation of success.

Additionally, certain claimed subject matter from the Nektar Patents involves certain inherent properties that require no express prior art disclosure. In particular, a POSA would have known that water could be used to consume, or react away, unreacted diaryl carbonate, such as di-BTC, in a solution, and that water was a key ingredient in many solvents. Thus, for example, a POSA would have understood that while a prior art reference may not explicitly state that water was used to consume unreacted di-BTC, water present in solvents added to a solution containing unreacted di-BTC would consume the unreacted di-BTC. A POSA also would have understood that the water would not react with mPEG-BTC in the solution as quickly as with unreacted di-BTC.

A. Combining an aprotic solvent with di(1-benzotryazolyl)carbonate and a hydroxy-terminated, water-soluble polymer such as mPEG (20,000 Da)-OH to produce an active carbonate ester and unreacted di(1-benzotryazolyl)carbonate was known.

PEG is a hydrophilic polymer which has considerable utility in biotechnology and medicine, as it is soluble in water and in many organic solvents and lacks both toxicity and immunogenicity. '604 patent at 1:18-22, 1:49-51; '462 patent at 2:45-55; 26:24-38. It is also used to covalently attach polymers to insoluble molecules to make PEG-molecule "conjugate[s]" soluble. '604 patent at 1:51-53; '462 patent at 2:56-60; '558 patent at 1:22-25. PEG is commonly used as mPEG, which is a hydroxy-terminated, water-soluble polymer that has the following structure:

'604 patent at 1:34-40; '462 patent at 4:1-13; '558 patent at 34-37. mPEG(20,000 Da)-OH is a form of mPEG with a molecular weight of 20,000 Da. '604 patent at 1:34-36, 2:32-34.

Coupling PEG with a molecule such as a protein often requires "activating" the PEG by preparing a derivative of the PEG having a functional group at a terminus thereof that can react with certain moieties on the protein, such as an amino group. '604 patent at 1:57-62; '462 patent at 9:62-10:23; 10:48-54; '558 patent at 1:34-44. mPEG-BTC, a 1-benzotriazolylcarbonate ester, is one such derivative. The prior art provided a method for preparing mPEG-BTC consisting of making a solution of mPEG(20,000 Da)-OH (0.001 moles), di-BTC (0.00803 moles), and the aprotic solvent acetonitrile (40 ml), then removing the solvent by distillation and dissolving the residue in methylene chloride and ethyl ether. '604 patent at Example 2. This method used significantly more di-BTC than mPEG(20,000 Da)-OH, which would result in unreacted di-BTC being present in the solution. *Id.*

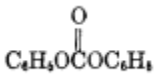
Thus, a POSA would have been motivated to combine an aprotic solvent with mPEG(20,000 Da)-OH to produce mPEG-BTC, with unreacted di-BTC left over.

B. A POSA would have been motivated to use a reactive molecule, including, for example, water, to consume the unreacted di(1-benzotryazolyl)carbonate

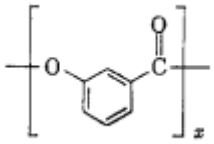
The Nektar Patents describe the use of water to remove unreacted di-BTC from solution as the problem the alleged inventions of these patents solves. *See, e.g.*, '489 patent at 3:61-4:23, 5:21-27, 12:35-43. However, consuming unreacted material was far from a novel concept in the art and was standard practice for a POSA. *See, e.g.*, Paul at 2096-99. More specifically, water was known to rapidly hydrolyze diaryl carbonates, such as di-BTC (*see infra*), particularly in basic environments. *E.g.*, Cooper at 3178-20. Many reactions in the prior art between polyethylene glycol and carbonates similar to di-BTC recognized that carbonates are sensitive to water, and were therefore performed in anhydrous conditions. *See, e.g.*, Elbert, at 181; Ji, at ¶ [0070]; Miron, at 568-69; Schiavon, at 125, 129; Nijs, at 88; Sartore, at 47; '100 patent, at 16:59-67. Water, in various forms – including in saturated $NaHCO_3$ solutions, solutions comprising water, or water-based solutions – was also well-known for working-up reactions that included di-BTC or similar carbonates. *See*, *e.g.*, Beauchamp, at 27; Ueda, at 908-909; GB 2 158 432 B, at 10:11-21; '549 patent, at 37:24-28. Based on this knowledge, a POSA would have been motivated to add water to a basic solution containing unreacted di-BTC, such as that resulting from step (a) of the claims (which is obvious for the reasons described above), in order to consume the remaining di-BTC in solution. A POSA would have further appreciated the following:

(i) Di-BTC is a Diaryl Carbonate

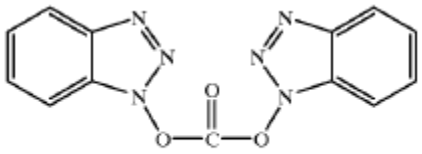
Diaryl carbonates are carbonate esters with aromatic substituents. Diphenyl carbonate is a simple diaryl carbonate, and has the following structure:



Cooper at 3718. Other aromatic esters may have the following structure:



Id. di-BTC was known to have the following structure:



di(1-benzotriazolyl)carbonate (diBTC)

'604 patent at 3:55-64. This structure of di-BTC is similar in structure to the diaryl carbonates discussed in Cooper. Accordingly, a POSA would have considered di-BTC to be a diaryl carbonate.

The prior art taught that using an excess of carbonate reagent was advantageous. *See, e.g.*, '604 patent, at 7:47-62; Beauchamp, at 27; Elbert, at 181-82; Miron, at 568-569; Schiavon, at 125, 129; Nijs, at 88; Paul; at 2096-99; Sartore, at 47; '100 patent, at 16:59-67.

(ii) <u>Diaryl Carbonates React Quickly with Water</u>

The prior art disclosed that diaryl carbonates hydrolyze very quickly in a variety of aqueous environments, and significantly faster than their alkyl counterparts. Cooper at 3718. Additionally, the reaction of diaryl carbonates, such as diphenyl carbonate, in basic media is "extremely fast." *Id*. at 3718-19. The prior art disclosed that diphenyl carbonate reacted at a rate of 8.4 x 10^{-1} l. mole^{-1}sec.$^{-1}$ in basic media, as compared to its reaction time in neutral (1.31 x 10^{-5} l. mole^{-1}sec.$^{-1}$)

or acidic (2.33×10^{-4} l. $mole^{-1}sec.^{-1}$) media. Cooper at 3719. The reaction between mPEG and di-BTC described in the '604 patent takes place in such a basic environment, as evidenced by the presence of the base pyridine. '604 patent at 7:47-53. Accordingly, a POSA would have been motivated to add water to a reaction mixture of mPEG and diaryl carbonate, such as di-BTC, to quickly hydrolyze any unreacted di-BTC.

(iii) Water May Be Added to a Solution to Consume Unreacted Activated Carbonate Reagent

Moreover, water had previously been used to consume unreacted activated carbonate reagent in a mixture, particularly through the use of solvents that contain water. A POSA, understanding these teachings, would have further understood that water would be a successful reactive molecule to remove excess di-BTC.

For example, the prior art disclosed adding $NaHCO_3$ to a mixture of monodispersed branched mPEG (1.21 mmol), acetonitrile (20 mL), disuccinimidyl carbonate (1.82 mmol), and triethylamine. WO '871 at 51:5-15. Excess disuccinimidyl carbonate was added to the mixture, as demonstrated by the mmol of disuccinimidyl carbonate added compared to the mmol of mPEG added. *Id.* $NaHCO_3$ is a solution of sodium hydrogen carbonate in water; thus, water was provided as a reactive molecule to consume unreacted activated carbonate reagent of the product mixture. Additionally, the presence of triethylamine indicates that the reaction media was basic.

As a further example, Paul describes an analogous reaction, using an excess of N,N'-carbonyl diimidazole. There, an excess of N,N'-carbonyl diimidazole with the carboxylic acid group of an amino acid to form an acylimidazole as activated intermediate. Paul, at 2096. Then, water is added to destroy the unreacted N,N'-carbonyl diimidazole. *Id.*

In further prior art, the solvents methylene chloride and ethyl ether were added to a composition of $mPEG_{20,000}$-OH and excess di-BTC, wherein both solvents were not specified as

water-free and inherently contain water; thus, water was provided to consume unreacted activated carbonate reagent of the product mixture. *See, e.g.*, '604 patent at Example 2; Merck Specification for Dichloromethane EMPLURA®, pg. 1; Merck Specification for Diethyl Ether EMPLURA®, pg. 1.

Water was common in workups following reactions involving di-BTC. *See, e.g.*, Ueda, at 908-09; GB 2 158 432, at 10:10-24; *see also, e.g.*, Beauchamp, at 27; '549 patent, at 37:8-45.

A POSA would thus have been motivated to use water to consume unreacted carbonate reagent in a basic solution containing mPEG.

(iv) The carbonyl carbon of a diaryl carbonate would react faster with water than that of mPEG-BTC

A POSA would not have been deterred from using water due to a risk that mPEG-BTC may also hydrolyze rapidly. The prior art disclosed that the reaction between mPEG-BTC and lysine to form di-N-PEGylated lysine occurs in aqueous media at a pH of 8.0 at "room temperature," indicating that mPEG-BTC has stability in water. *See, e.g.,* '604 patent at 7:63-8:16. The prior art further disclosed that, in aqueous media at pH of 8.0 and 25ºC, the hydrolysis of mPEG-BTC has a half-life of 13.5 minutes. *See, e.g.,* Shearwater Catalog at 45. A POSA would have recognized that this half-life was far from the "extremely fast" hydrolysis of diaryl carbonates disclosed in the prior art. Cooper at 3718-20. Thus, a POSA would have been motivated to use water to consume unreacted di-BTC.

C. Reacting the active carbonate esters with water-soluble polymer lysine to form polymeric lysine derivatives was known

The prior art disclosed that PEG-BTC esters can be reacted with lysine to form a polymeric lysine derivative. '604 patent at 6:46-48; '462 patent at 12:40-15:54. The prior art further described reacting the active carbonate ester mPEG-BTC with lysine HCl to produce a mixture of di-N-PEGylated lysine, mono-N-PEGylated lysine, and $mPEG_{20,000}$. '604 patent at 7:63-8:16.

Thus, a POSA would have been motivated to react mPEG-BTC with lysine to form a polymeric lysine derivative.

D. Reacting the polymeric lysine derivatives to form polymeric reagents was known

The prior art disclosed reacting purified mPEG-disubstituted lysine (a polymeric lysine derivative) with N-hydroxysuccinimide to produce mPEG-disubstituted lysine activated as the succinimidyl ester. '462 patent at 28:32-59. The prior art further disclosed that mPEG-disubstituted lysine activated as the succinimidyl ester reacts with amino groups in enzymes under mild aqueous conditions – i.e., that it is a polymeric reagent. '462 patent at 9:62-65. Thus, a POSA would have been motivated to react mPEG-BTC to form polymeric reagents.

E. Reacting the polymeric reagents with an active agent under conjugation conditions to form water-soluble polymer-active agent conjugates was known

The prior art disclosed modifying enzymes with activated, two-armed, mPEG-disubstituted lysine that had been activated as the succinimidyl ester. *Id.*at 30:65-31:26. Thus, a POSA would have been motivated to react a polymeric reagent – mPEG-disubstituted lysine activated as the succinimidyl ester – with an active agent under conjugation conditions to form water-soluble polymer-active agent conjugates.

F. Exemplary combinations of invalidating prior art

In sum, the prior art listed above would have rendered claims of the '784 patent, the '306 patent, the '489 patent, and the '295 patent obvious to a POSA. Non-limiting, exemplary combinations of the prior art are identified below for each asserted patent. The references below and identified in Exhibits A, B, C, and D may be supplemented or substituted with similar teachings in additional references.

(i) The ’784 patent

As set forth in Exhibit A, claim 1 of the ’784 patent is invalid for obviousness under 35 U.S.C. § 103. UCB identifies the following as exemplary invalidating combinations of prior art:

- The ’604 patent alone, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the ’549 patent, WO ’871, or Paul
- The ’604 patent in view of WO ’871, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the ’549 patent, WO ’871, or Paul

As explained in, at least, Sections VI.A-B above (whose literature references are incorporated here by reference), and shown in Exhibit A, the above-listed combinations of prior art render the claims obvious. For example, the ’604 patent taught a POSA each element of the claim of the ’784 patent. To the extent any specific claim element of the ’784 patent is asserted not to have been obvious to a POSA in light of the ’604 patent, the following references, when read in combination with the ’604 patent and/or each other, would have rendered claims obvious: WO ’871; Cooper; and/or the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, or Paul. As shown in Exhibit A, each of these references taught, or otherwise motivated a POSA to make, the claimed subject matter.

In addition, other combinations of prior art references render the claims obvious. For example, combination of any of the prior art and/or prior art teachings identified in §§VI.A. – VI.B. *supra*, which correspond to the elements of the claim of the ‘784 patent, would have rendered the claim obvious. UCB expressly reserves the right to rely on any combination of these disclosures at any appropriate time.

A POSA would have read these prior art references in view of the POSA's knowledge and expertise in the field. Thus, to the extent a claim element is asserted not to have been explicitly taught in a prior art reference, a POSA's knowledge and skill in the art would allow them to draw inferences from the prior art references. Additionally, a POSA would have understood that certain claim elements of the '784 patent were related to inherent properties, for which no prior art showing was necessary.

(ii) The '306 patent

As set forth in Exhibit B, claims 1, 2, and 4 of the '306 patent are invalid for obviousness under 35 U.S.C. § 103. UCB identifies the following as exemplary invalidating combinations of prior art:

- The '604 patent alone, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul
- The '604 patent in view of WO '871, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul

As explained in, at least, Sections VI.A-C above (whose literature references are incorporated here by reference), and shown in Exhibit B, the above-listed combinations of prior art render the claims obvious. For example, the '604 patent taught a POSA each element of the claims of the '306 patent. To the extent any specific claim element of the '306 patent is asserted not to have been obvious to a POSA in light of the '604 patent, the following references, when read in combination with the '604 patent and/or each other, would have rendered the claims obvious: WO '871; Cooper; and/or the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, or

Paul. As shown in Exhibit B, each of these references taught, or otherwise motivated a POSA to make, the claimed subject matter.

A POSA would have read these prior art references in view of the POSA's knowledge and expertise in the field. Thus, to the extent a claim element is asserted not to have been explicitly taught in a prior art reference, a POSA's knowledge and skill in the art would allow them to draw inferences from the prior art references. Additionally, a POSA would have understood that certain claim elements of the '306 patent were related to inherent properties, for which no prior art showing was necessary.

(iii) The '489 patent

As set forth in Exhibit C, claims 1, 2, and 4 of the '489 patent are invalid for obviousness under 35 U.S.C. § 103. UCB identifies the following as exemplary invalidating combinations of prior art:

- The '604 patent in view of the '462 patent, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul
- The '604 patent in view of the '462 patent and WO '871, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul

As explained in, at least, Sections VI.A-E above (whose literature references are incorporated here by reference), and shown in Exhibit C, the above-listed combinations of prior art render the claims obvious. For example, the '604 patent and the '462 patent taught a POSA each element of the claims of the '489 patent. To the extent any specific claim element of the '489 patent is asserted not to have been obvious to a POSA in light of the '604 patent and the '462

patent, the following references, when read in combination with the '604 patent and the '462 patent would have rendered the claims obvious: WO '871; Cooper; and/or the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, or Paul. As shown in Exhibit C, each of these references taught, or otherwise motivated a POSA to make, the claimed subject matter.

A POSA would have read these prior art references in view of the POSA's knowledge and expertise in the field. Thus, to the extent a claim element is asserted not to have been explicitly taught in a prior art reference, a POSA's knowledge and skill in the art would allow them to draw inferences from the prior art references. Additionally, a POSA would have understood that certain claim elements of the '489 patent were related to inherent properties, for which no prior art showing was necessary.

(iv) The '295 patent

As set forth in Exhibit D, claims 1, 2, and 4 of the '295 patent are invalid for obviousness under 35 U.S.C. § 103. UCB identifies the following as exemplary invalidating combinations of prior art:

- The '604 patent in view of the '462 patent, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul
- The '604 patent in view of the '462 patent and WO '871, optionally in view of Cooper, optionally in view of the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, the '549 patent, WO '871, or Paul

As explained in, at least, Sections VI.A-E above (whose literature references are incorporated here by reference), and shown in Exhibit D, the above-listed combinations of prior art render the claims obvious. For example, the '604 patent and the '462 patent taught a POSA

each element of the claims of the '295 patent. To the extent any specific claim element of the '295 patent is asserted not to have been obvious to a POSA in light of the '604 patent and the '462 patent, the following references, when read in combination with the '604 patent and the '462 patent would have rendered the claims obvious: WO '871; Cooper; and/or the Shearwater Catalog, Ueda, GB 2 158,432, Beauchamp, or Paul. As shown in Exhibit D, each of these references taught, or otherwise motivated a POSA to make, the claimed subject matter.

A POSA would have read these prior art references in view of the POSA's knowledge and expertise in the field. Thus, to the extent a claim element is asserted not to have been explicitly taught in a prior art reference, a POSA's knowledge and skill in the art would allow them to draw inferences from the prior art references. Additionally, a POSA would have understood that certain claim elements of the '295 patent were related to inherent properties, for which no prior art showing was necessary.

VII. THE CLAIMS OF THE NEKTAR PATENTS ARE INVALID UNDER 35 U.S.C. § 112

UCB provides below an identification of Nektar patent claims that are invalid pursuant to 35 U.S.C. § 112 as indefinite, not enabled, or lacking a sufficient written description. A more detailed basis for UCB's Section 112 positions will be set forth in UCB's expert reports on invalidity, to be served in accordance with the Court's Scheduling Order. UCB has not yet taken any depositions related to these issues. UCB specifically reserves the right to amend and/or supplement these Invalidity Contentions based on a failure to comply with 35 U.S.C. § 112. Below are exemplary Nektar patent claims that are invalid pursuant to 35 U.S.C. § 112:

A. U.S. 7,767,784

Claim 1 of the '784 patent is invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to make and use the claimed subject matter with respect to substantially consuming the excess, unreacted di-BTC.

Claim 1 of the '784 patent is invalid under 35 U.S.C. § 112 because the term "substantially all of the unreacted di(1-benzotriazolyl) carbonate is substantially consumed" is indefinite.

B. U.S. 8,193,306

Claims 1, 2, and 4 of the '306 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to make and use the claimed subject matter with respect to substantially consuming the excess, unreacted di-BTC.

Claims 1, 2, and 4 of the '306 patent are invalid under 35 U.S.C. § 112 because the term "substantially all of the unreacted di(1-benzotriazolyl) carbonate is substantially consumed" is indefinite.

Claims 1, 2, and 4 of the '306 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

Claims 1, 2, and 4 of the '306 patent are invalid because the patent does not provide a written description of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

C. U.S. 8,461,295

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to make and use the claimed subject matter with respect to substantially consuming the excess, unreacted di-BTC.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the term "substantially all of the unreacted di(1-benzotriazolyl) carbonate is substantially consumed" is indefinite.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the active carbonate ester of a water-soluble polymer lysine to form a polymeric lysine derivative" step.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not provide a written description of the "reacting the active carbonate ester of a water-soluble polymer lysine to form a polymeric lysine derivative" step.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not provide a written description of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate" step.

Claims 1, 2, and 4 of the '295 patent are invalid under 35 U.S.C. § 112 because the patent does not provide a written description of the "reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate" step.

D. U.S. 8,809,489

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to make and use the claimed subject matter with respect to substantially consuming the excess, unreacted di-BTC.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the patent does not provide a written description of the "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" step.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the patent does not enable one of ordinary skill in the art to practice the full scope of the "reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate" step.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the patent does not provide a written description of the "reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate" step.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the term "substantially all of the unreacted di(1-benzotriazolyl) carbonate is substantially consumed" is indefinite.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the term "reacting the polymeric lysine derivative in one or more reactions to form a polymeric reagent" is indefinite.

Claims 1, 2, and 4 of the '489 patent are invalid under 35 U.S.C. § 112 because the term "reacting the polymeric reagent with an active agent under conjugation conditions to thereby result in a water-soluble polymer-active agent conjugate" is indefinite.

VIII. CLAIMS OF THE NEKTAR PATENTS ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

A. Claim 1 of the '784 patent is invalid for double-patenting

Claim 1 of the '784 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 1, 6, 9, 12, 13, 14, 16, 17, and 18 of U.S. Patent No. 6,376,604;
- Claims 1, 2, 3, 4, 5, 11, 12, 13, and 15 of U.S. Patent No. 6,624,246;
- Claims 1 and 3-19 of U.S. Patent No. 7,101,932;
- Claims 1, 15, 16, 20, 21, and 22 of U.S. Patent No. 7,378,469;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claim 1 of U.S. Patent No. 8,193,306;
- Claim 1 of U.S. Patent No. 8,461,295;
- Claim 1 of U.S. Patent No. 8,563,651;
- Claim 1 of U.S. Patent No. 8,809,489;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

B. Claims 1, 2, and 4 of the '306 patent are invalid for double patenting

Claim 1 of the '306 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 17, 18, and 19 of U.S. Patent No. 6,624,246;
- Claims 20-22 of U.S. Patent No. 7,101,932;

- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-6 of U.S. Patent No. 8,299,173;
- Claim 1 of U.S. Patent No. 8,461,295;
- Claims 1-3 of U.S. Patent No. 8,563,651;
- Claim 1 of U.S. Patent No. 8,809,489;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 2 of the ’306 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 17, 18, and 19 of U.S. Patent No. 6,624,246;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1 and 2 of U.S. Patent No. 8,461,295;
- Claims 1-3 of U.S. Patent No. 8,563,651;
- Claims 1 and 2 of U.S. Patent No. 8,809,489;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 4 of the ’306 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 17, 18, and 19 of U.S. Patent No. 6,624,246;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-6 of U.S. Patent No. 8,299,173;
- Claims 1 and 2 of U.S. Patent No. 8,461,295;
- Claims 1-3 of U.S. Patent No. 8,563,651;

- Claims 1 and 2 of U.S. Patent No. 8,809,489;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

C. Claims 1, 2, and 4 of the '295 patent are invalid for double patenting

Claim 1 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claim 27 of U.S. Patent No. 7,101,932;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 2 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 4 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claim 27 of U.S. Patent No. 7,101,932;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and

- Claims 1-3 of U.S. Patent No. 9,839,695.

D. Claims 1, 2, and 4 of the '489 patent are invalid for double patenting

Claim 1 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claim 27 of U.S. Patent No. 7,101,932;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 2 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

Claim 4 of the '295 patent is invalid for double patenting over, at least, the following, in view of the prior art:

- Claim 27 of U.S. Patent No. 7,101,932;
- Claims 1-3 of U.S. Patent No. 7,544,738;
- Claims 1-4 of U.S. Patent No. 8,563,651;
- Claims 1-3 of U.S. Patent No. 8,816,002; and
- Claims 1-3 of U.S. Patent No. 9,839,695.

IX. DOCUMENT PRODUCTION ACCOMPANYING INITIAL INVALIDITY CONTENTIONS

Pursuant to Paragraph 4 of the Scheduling Order, UCB is providing a copy of each item of identified prior art that does not appear in the file histories of the Nektar Patents. A diligent search continues for other documents, and UCB reserves the right to supplement its production.

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/s/ Anthony D. Raucci

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December 23, 2020

CERTIFICATE OF SERVICE

I hereby certify that on December 23, 2020, copies of the foregoing were caused to be served upon the following in the manner indicated:

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EXHIBIT B

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February 9, 2021

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CONFIDENTIAL

VIA EMAIL

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Re: *UCB Pharma S.A., et al. v. Nektar Therapeutics*, No. 20-cv-650-CFC (D. Del.)

Tiffany:

We write in response to your January 29, 2021 letter.

UCB disagrees that its invalidity contentions are lacking in any way. The disclosure in UCB's contentions meets – or exceeds – the requirements set forth in the Scheduling Order. Indeed, UCB's contentions fairly put Nektar on notice of UCB's invalidity positions. Nektar's allegations to the contrary are without merit. (UCB reserves all rights to take appropriate action against Nektar's inadequate Responses to Plaintiffs' Invalidity Contentions.)

However, even if UCB's contentions were lacking in detail (a counterfactual assumption), a motion to strike would be inappropriate at this early stage of the case. Nektar can seek additional information on UCB's invalidity positions without any prejudice to its case and without unnecessarily burdening the Court. Nevertheless, UCB addresses Nektar's stated concerns below.

Nektar first suggests that UCB's identification of prior sales or offers for sale are inadequate because they "fail to provide any evidence or analysis to support their position that there was a sale or offer for sale of 'PEG generated, in part, via the processes claimed' in the patents-in-suit." (Letter at 1.) After acknowledging that discovery is necessary for this issue, Nektar suggests UCB "should have identified and promptly sought the allegedly necessary discovery." (*Id.* at 2.)[1] Nektar thus seemingly suggests that UCB should have completed its

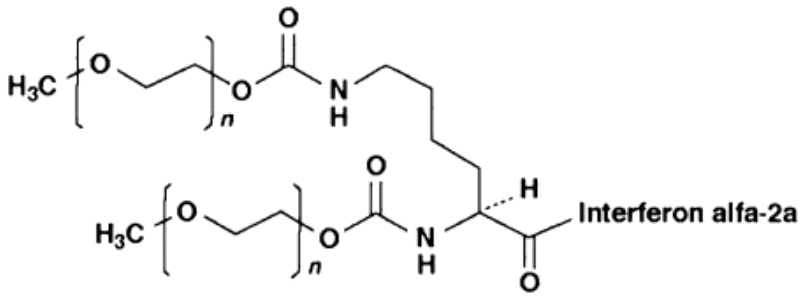
[1] UCB has pending discovery requests for this information. (*E.g.*, UCB Pharma S.A.'s and Celltech R&D Limited's First Set of Requests for Production of Documents, ESI, and Things (Nos. 1-45), Document Request No. 22; Plaintiffs' First Set of Interrogatories, Interrogatory

discovery sometime in the very infancy of this case (*i.e.*, sometime in the two-weeks between the Scheduling Order's entry and the initial invalidity contentions).

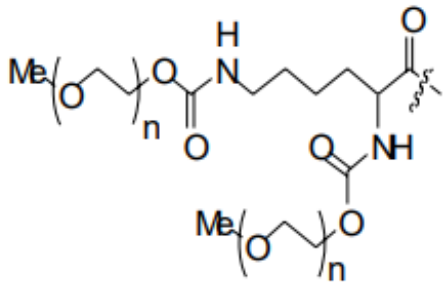
Nektar is wrong. The Scheduling Order allows fact discovery much later than the initial invalidity contentions. In fact, fact discovery need only "be initiated so that it will be completed on or before September 3, 2021." (D.I. 18, § 7(a).) Nektar's attempt to force UCB into accelerated discovery is inappropriate.

Nektar's position is also disingenuous. As Nektar knows, the process for manufacturing PEG associated with any given product is not publicly disclosed. But, there are good reasons to believe that the list of PEGylated products in UCB's contentions may constitute prior anticipatory sales or offers for sale. Consider, for example, Pegasys® and Macugen®, whose PEG structures, respectively, are:

Pegasys®



Macugen®



and n is approximately 450.

(*See* K. Rajender Reedy, *et al.*, *Use of peginterferon alfa-2a (40K) (Pegasys®) for the treatment of hepatitis C*, 54 ADVANCED DRUG DELIVERY REVIEWS 571-586 (2002); Macugen® Label, at 2 (Sept. 17, 2004).) Pegasys®'s and Macugen®'s PEGs are structurally similar to that described in the Nektar Patents. Nektar has made it clear that it sold PEG to Hoffmann-La Roche for Pegasys® as early as February 1997 (*see* Nektar Therapeutics, 10-K (Mar. 16, 2006) ("We entered into a

No. 7.) Rather than promptly providing such information, Nektar requested an extension. (*See* Email from Tiffany Mahmood to UCB's counsel (Feb. 3, 2021).)

license, manufacturing and supply agreement in February 1997 with F. Hoffmann-La Roche Ltd. whereby we license to Roche the PEG reagent used in Roche's PEGASYS®[.]")), and to Eyetech Pharmaceuticals, Inc. for Macugen® as early as February 2002 (*id.* ("We entered into a license, manufacturing and supply agreement with Eyetech Pharmaceuticals, Inc. in 2002, whereby we provide one of our PEG reagents for the development and commercial manufacturing of Macugen®[.]")). Nektar claims to manufacture similar PEG (such as the PEG in Cimzia®) via the process disclosed in the Nektar Patents. UCB may therefore examine whether (and, if so, when) Nektar sold or offered to sell PEG for Pegasys®, Macugen®, or any of the other products described in UCB's contentions via the process claimed in the Nektar Patents.

Separately, Nektar's position is inconsistent with the Scheduling Order, which requires only that UCB identify "the item offered for sale or publicly used or known, the date the offer or use took place or the information became known, and the identity of the person or entity which made the use or which made and received the offer[.]" (D.I. 18, § 3(a).) UCB provided that information. Nektar's demand for further information – such as "all evidence and analysis in [UCB's] possession at this time" – is inappropriate. *See, e.g., Ethanol Boosting Sys., LLC v. Ford Motor Co.*, No. 1:19-cv-196, D.I. 45-1, Exhibit 3, at 51:11-18 (D. Del.) (noting that contentions need not "set forth each and every piece of evidence").

Nektar also suggests that UCB's Section 112 contentions "run[ ] afoul of the Court's requirements." (Letter at 2.)[2] In support of this position, Nektar cites a single instance from the contentions: UCB's assertion "that '[c]laim 1 of the '784 patent is invalid under 35 U.S.C. § 112 because the term 'substantially all of the unreacted di(1-benzotriazolyl) carbonate is substantially consumed' is indefinite.'" (*Id.*) According to Nektar, UCB made "no reference to the specification or how the claim term is supposedly indefinite." (*Id.*)

Nektar's argument is misplaced. Identifying the specific limitation and the reason the limitation renders the claim invalid, *e.g.*, indefiniteness, as UCB did, satisfies the Scheduling Order's requirements, and is certainly enough information for Nektar to understand UCB's position. Despite that disclosure, Nektar seems to believe that UCB's contentions should have contained more detail, something akin to an expert report. That belief is incorrect. The Scheduling Order requires only that UCB identify "[a]ny grounds of invalidity based on . . . indefiniteness under 35 U.S.C. § 112(b), or lack of enablement or insufficient written description under 35 U.S.C. § 112(a)." (D.I. 18, § 3(d).) Other portions of the Scheduling Order – such as sections 3(a) and 3(b) related to anticipation and obviousness under 35 U.S.C. §§ 102 and 103 – require further detail of the stated position. Section 3(d) does not.

Moreover, Nektar's position undermines other aspects of the Scheduling Order. Sections 13, 14, and 15 describe a procedure for claim construction disputes, including the identification of "supporting intrinsic evidence" for each party's position. (D.I. 18, §§ 13-15.) While the Court does not address indefiniteness arguments as part of claim construction, UCB will include that information, as necessary, in the claim construction exchanges to preserve its right to raise it at the appropriate time. And, as part of that procedure, the parties need not exchange such intrinsic evidence until March 5, 2021. (*Id.*, § 13.) Nektar's attempt to force UCB to make "reference to

[2] Nektar failed to explain why it believes any of UCB's Section 112 contentions, beyond indefiniteness, are allegedly inadequate.

the specification" in its December 23, 2020 invalidity contentions is inappropriate. Separately, the Scheduling Order requires UCB to submit opening expert reports on November 15, 2021. (*Id.*, § 17(a).) UCB need not provide expert-report-level detail before that time.

Nektar also suggests that UCB's obviousness-type double patenting disclosure was insufficient because it "only provide[d] a list of claims and patents that they believe render certain claims of the patents-in-suit invalid for obviousness-type double patenting." (Letter at 2.) Nektar's position, however, is based on a mistaken premise. The Scheduling Order requires UCB to disclose certain, specific information in its initial invalidity contentions: anticipation and obviousness under 35 U.S.C. §§ 102 and 103 (D.I. 18, §§3(a), (b)) and "grounds based on 35 U.S.C. § 101, indefiniteness under 35 U.S.C. § 112(b), or lack of enablement or insufficient written description under 35 U.S.C. § 112(a) (*id.*, § 3(d)). The Scheduling Order does not expressly contemplate disclosure of obviousness-type double patenting contentions, or require any specificity with respect to such contentions. UCB identified references patents and claims as a courtesy.

Regardless, obviousness-type double patenting requires an "analysis of the claims of the earlier-expiring patent (or reference patent) and the later-expiring patent (including their differences) and whether the differences in subject matter between the claims render them patentably distinct." *In re Biogen's '755 Patent Litig.*, No. 10-cv-2734, 2018 WL 3586271, at *11 (D. Del. July 26, 2018) (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001)). By disclosing specific reference patents and claims, UCB provided enough information for Nektar to understand its position.

Nektar finally suggests that UCB "hinder[ed]" its "ability to respond to [UCB's] invalidity defenses" because UCB did not provide a "definition for a person of ordinary skill in the art." (Letter at 2.) This complaint, however, lacks any legal basis. First, the Scheduling Order does not require UCB to provide that information in its invalidity contentions. (*See* D.I. 18, §§ 3(a)-(d).) Second, UCB provided its initial invalidity contentions on December 23, 2020, but Nektar did not raise this as a potential issue until January 29, 2021 – over a month later and the same day its responses to the invalidity contentions were due. If Nektar was truly "hinder[ed]" by the lack of this information, it could have requested it in a timely fashion.

Given the foregoing, Nektar has no grounds to seek any judicial relief at this time, and certainly not a motion to strike. In any event, we are available to meet and confer on February 11, 2021 from 10 am – 1 pm EST, February 12, 2021 from 11 am – 3 pm EST, or we can find a convenient time next week.

Sincerely,

/s/ *Eric Majchrzak*

Eric Majchrzak